UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/765,588	04/25/97	HAYWARD	N 10441

EXAMINER

HM11/0105

SCULLY SCOTT MURPHY & PRESSER
400 GARDEN CITY PLAZA
GARDEN CITY NY 11530

ART UNIT	PAPER NUMBER
1646	13

DATE MAILED: 01/05/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 19 October 1998

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-42 is/are pending in the application.
Of the above, claim(s) 1-25, 34, 37-42 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 26-33, 35-36 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

~~☒ received.~~
☐ received in Application No. (Series Code/Serial Number) _____.
☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3,4
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-421-632/40206

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group II, claims 26-33 and 35-36 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that pursuant to 37 C.F.R. §§ 1.111 and 1.143, the inventions must be shown to be independent and distinct and without such a showing, the restriction is unauthorized (see response at page 3). This is not found persuasive because 37 C.F.R. §§ 1.111 and 1.143 are not applicable to the instant situation because the application was filed under 35 U.S.C. § 371, and the claims are considered with regard to Unity of Invention.

Applicant further argues that the claims of Groups I, II and III are characterized at least by the technical feature defined by SEQ ID NO:2. This argument is not persuasive, because in order for the claims to have Unity of Invention, they must all share the same special technical feature. A special technical feature means those technical features that define a contribution over the prior art. (See M.P.E.P. 1850.) Applicant's own specification states that SEQ ID NO:2 corresponds to human VEGF (see page 4 of specification at line 11-12), which was clearly known in the prior art (see page 1 of specification at lines 23-30).

At pages 4-5 of the response, Applicant argues that restriction of the claims will impose a financial burden on Applicant's. This fact is appreciated, but not a proper rebuttal of the holding of Lack of Unity of the claims. At page 6 of the response, Applicant argues that the claims "can be vulnerable to legal challenges alleging double patenting". This fact is also appreciated, however, this is not a proper rebuttal of the holding of Lack of Unity of the claims.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-25, 34 and 37-42 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 11.

Oath/Declaration

3. The Declaration is objected to because it has an address for the inventor Gunther Weber which is illegible. It appears that the Post Office Address was corrected with correction fluid, but the previous address is showing through, which makes the correct address illegible. Correction is necessary.

Priority

4. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Drawings

5. Figure 8 of the instant application is presented on separate pages. Although Figures 8A and 8B are correctly labeled according to 37 C.F.R. § 1.84 (U)(1), which requires that when partial views of a drawing which are intended to form one complete view must be identified by the same number followed by a capital letter, the Brief Description of the Drawings at page 10 does not properly refer to the Figures, in that lower case letters are used. Correction is required.

Figures 1-6, 9-11, and 16-17 of the instant application are presented in separate panels or on separate pages. 37 C.F.R. § 1.84(u) (1) states that when partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the **same number followed by a capital letter**. The instant application uses the format of a number followed by lower case roman numerals. Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84(u) (1), the specification should be amended to change the Brief Description of the Drawings and the rest of the specification accordingly. If, for example, Figure 1 is divided into Figures 1A, 1B, 1C, and 1D, then the Brief Description and all references to this figure in the specification must refer to Figures 1A, 1B, 1C and/or 1D.

Specification

6. The title of the invention is not descriptive (i.e. "Novel growth factor ..."). A new title is required that is clearly indicative of the invention to which the claims are directed.

Sequence Compliance

7. The claims do not comply with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. Claim 33 refers to a sequence as set for in Figure 9, which is improper. Correction is required. See M.P.E.P. 2422.03.

8. Applicant should note that claims 30-31 depend from a nonelected claim (claim 1). However, in order to advance prosecution, these claims are being examined as if they are directed to nucleic acid molecules encoding the proteins of claim 1. In light of this interpretation, claim 30 appears to be duplicative of claim 26. In the event that claim 26 is found to be allowable, claim 30 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 26-33 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims fail to include any limitations which would distinguish the nucleic acids from one which occurs in nature. In the absence of the hand of man, the naturally occurring nucleic acid molecules and proteins are considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Additionally, mere purity of a naturally occurring product does not necessarily impart patentability. Ex parte Siddiqui, 156 USPQ 426 (1966). However, when purity results in a new utility, patentability is considered. Merck Co. v. Chase Chemical

Co., 273 F. Supp. 68 (1967). Filing of evidence of a new utility imparted by the increased purity of the claimed invention and amendment of the claims to recite a purity limitation, if supported by the specification, is suggested to obviate this rejection. Applicant should point to the basis in the specification for any amendment to the claims.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 26-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid molecules which encode a protein or polypeptide, does not reasonably provide enablement for nucleic acid molecules which encode "a proteinaceous molecule". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The recitation of "proteinaceous molecule" in the claims does not convey the concept of a protein or polypeptide. Instead, it can be interpreted as a molecule that includes protein as part of its constitution. This would include molecules that are derivatized proteins, etc. However, a nucleic acid molecule is not capable of encoding a derivatized protein. Therefore, the claims are only enabled for nucleic acid molecules which encode proteins, polypeptides, peptides, etc.

13. Claims 26-33 and 35-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid molecules which encode naturally occurring VEGF molecules and are capable of inducing vascularization, interacting with a receptor, inducing cell migration, survival, or astroglial cell proliferation, does not reasonably provide enablement for nucleic acid molecules which encode proteinaceous molecules which have at least about 15% similarity to SEQ ID NO:2 and retain the biological activity of the protein of SEQ ID NO:2 or have an amino acid sequence substantially as set forth in the various SEQ ID NOs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The instant claims encompass nucleic acid molecules which encode a protein that retains as little as 15% similarity (not even identity) to the naturally occurring VEGF of SEQ ID NO:2, but which also retains the biological activity of VEGF. However, the instant specification only discloses the isolation of a single molecule which meets the limitations of these claims, other than the known VEGF proteins of the prior art. The instant specification provides no guidance as how to modify the disclosed proteins and obtain a protein which has the biological activity of the native VEGF disclosed (SEQ ID NO:2). The specification provides no guidance as to which amino acids (i.e. structural elements) of the native proteins are critical to the biological activity which is recited in the claims. Without this type of guidance, the skilled artisan does not have a reasonable expectation of mutating the VEGF of SEQ ID NO:2 and obtaining a functional protein that retains a biological activity of the native protein. One may argue screening for bioactivity could be done, however, this is basically a "wish to know" and the standard for an enabling disclosure is

not one of making and testing. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them, then the instant application does not support the breadth of the claims.

A review of *In re Wands* clearly points out the factors to be considered in determining whether a disclosure would require undue experimentation and include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of these factors are considerations when determining the enablement of an invention. The claims encompass a limitless number of embodiments because they recite no structural limitations on the VEGF due to the recitation of at least about 15% similarity (only that they have one of 3 biological properties of VEGF of SEQ ID NO:2) (factor 1). The specification provides no guidance as to amino acid positions and/or regions which would provide the recited bioactivity of VEGF (factor 2) and provides no examples of any VEGF polypeptides other than the native proteins (factor 3). Additionally, the specification provides no VEGF molecules which differ by as much as the contemplated 85% and still retain biological activity other than naturally occurring proteins. The claims encompass molecules wherein 85% of the amino acid sequence is missing, however, one of ordinary skill in the art would not reasonably expect that a molecule that meets this limitation of the claims to be sufficient for biological activity, such as receptor binding

or activation. The claims are exceedingly broad because they only require at least about 15% similarity, which means that not a single amino acid need be the same, but only similar (factor 8). In addition, although the skill in the art is known to be high (factor 6), the results of mutating amino acids to produce a function protein is highly unpredictable (factors 4, 5 and 7). Therefore, in light of this analysis, one would reasonably conclude that the breadth of the instant claims is not commensurate in scope with the specification, absent evidence to the contrary.

14. Claim 36 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a protein wherein the nucleic acid molecule comprises a sequence that encodes a protein, does not reasonably provide enablement for methods which use nucleic acid sequences which hybridize to a disclosed sequence wherein there is no requirement for the hybridizing sequence to encode a protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claim encompasses a method of making a protein using a nucleic acid molecule that "is capable of hybridising under low stringency conditions to a reverse complement of the nucleotide sequence as set forth in SEQ ID NO:3". However, there is no limitation in the claim that requires the hybridizing sequence to encode a protein. There are a multitude of sequences that would be capable of hybridizing to the disclosed sequence under low stringency conditions, but they would not be useful in a method of making a protein unless they actually encoded a protein. Furthermore, the instant specification fails to teach how to make a protein with a nucleic

acid molecule that does not encode a protein. Therefore, the instant claim is not enabled for the claimed breadth for the reasons provided.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 26-33 and 35-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 recites that the proteinaceous molecule exhibit "at least one property in common" with VEGF. However, there is no indication of what properties are to be encompassed, or to which VEGF the molecule is to be compared. There are several different VEGFs known in the prior art, as well as several different splice variants (see Houck et al. Mol. Endocrinol. 5: 1806-1814, 1991). Therefore, one of ordinary skill in the art would not know which properties (be them biological or physical) are intended by the claims or which VEGFs are intended by the claims. Because of this, one cannot determine the metes and bounds of the claims, making them indefinite.

Claims 26, 31-32, and 35-36 recite percent similarity. However, the use of % identity or similarity is indefinite without a recitation of an algorithm for calculating this identity. In determining identity, there are a number of variables which must be selected and are necessary for the calculation of identity. Based on the selection of values for these variables, the % identity can

vary immensely. For example, consider two sequences: acgtac and acac. These can be compared in any of four ways.

acgtac	4/6=67%	acgtac	2/6=33%
|| ||		||	
ac--ac	4/4=100%	acac	2/4=50%

Depending how gaps and lengths are calculated, the percent identity between these two simple sequences can vary from 100% to 33%. In addition, the reference George et al. is provided with this Office action which demonstrates the numerous types of algorithms which can be used to calculate identity and how selection of values for the variables will influence this calculation (i.e. gaps, lengths, etc.). As taught by George et al., "[t]he results of the analysis are entirely dependent on the choice of scoring rules" (see page 130). Therefore, the recitation of %identity without the provision of a specific algorithm in the instant specification as how this identity is to be calculated is indefinite and the metes and bounds of the claims cannot be determined.

Claims 29 and 33 recite a sequence "substantially as set forth", however, the metes and bounds of such a sequence cannot be determined because it is not clear how much variation from the recited sequence would be encompassed by "substantially as set forth". If the use of this phrase is to convey "variants thereof", it does not readily perform that function. Therefore, the claims are indefinite and unclear.

Claims 30-31 depend from non-elected claim 1, therefore, it is not clear what is being claimed. Furthermore, claim 1 does not provide antecedent basis for the term "nucleic acid molecule" in claims 30-31.

Claims 32 and 36 recite nucleic acid molecules which are "capable of hybridising under low stringency conditions". There are several factors which affect the hybridization of nucleic acid molecules and there are a multitude of conditions which may or may not be considered stringent because stringency is a relative condition. Without some sort of guidance or definition in the claims of what this term is meant to encompass, the metes and bounds of the claims cannot be determined, thereby making the claims indefinite.

Claim 33 is directed to a nucleic acid molecule which encodes "a murine homologue of human VEGF". This claim is unclear and indefinite because it is not clear which "human VEGF" is intended, thereby making the recitation of "a murine homologue" unclear and indefinite because the metes and bounds of the claim cannot be determined. As stated above, there are several different forms and versions of VEGF in the art, and without knowing to which one the claim is referring, one cannot determine if they have a murine homologue or not. This is especially true in light of the claim language of "comprising a nucleotide sequence substantially as set forth in Figure 9" because the nucleic acid sequence is not necessarily the one that is present in the figure.

Claim 36 is confusing in that it is not clear what the constitution of "the nucleotide sequence" is from the claim. The claim recites that the nucleotide sequence is "as set forth in SEQ ID NO:3", but then further states that "the nucleotide sequence has at least 15% similarity but at least 30% dissimilarity to the nucleotide sequence set forth in SEQ ID NO:3". Therefore, it is not clear if "the nucleotide sequence" has the sequence of SEQ ID NO:3 or if it is different from that sequence, making the claim indefinite.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

18. Claims 26-28, 30-31 and 35-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Tischer et al. (U.S. Pat. No. 5,194,596).

Tischer et al. teach a nucleic acid molecule which encodes a VEGF protein (see Figure 7). Because this protein is a VEGF, it would necessarily have a property of VEGF, including the ability to induce astroglial proliferation, as recited in claim 28 and demonstrated by Figures 16 and 17 of the instant application. The protein of Figure 7 of Tischer et al. has approximately 85% similarity to SEQ ID NO:2 of the instant application, thereby meeting the limitations of claims 26, 31 and 35. This is due to the additional amino acids of SEQ ID NO:2, since there is 100% identity over a span of 165 amino acids (see sequence comparison attached to reference). The protein is a human protein, thereby meeting the limitation of claim 30. Tischer et al. further teach the recombinant production of the VEGF protein (see Example 8, beginning at column 30), meeting the limitations of claim 35. Therefore, the instant claims are anticipated by Tischer et al.

Claims 26, 32 and 35-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Tischer et al. (U.S. Pat. No. 5,194,596).

Claims 32 and 36 require the claimed nucleic acid molecule to have sequence similarity to SEQ ID NO:3 (15% similarity or hybridize and have sequence similarity). Tischer et al. teach a nucleic acid molecule encoding a VEGF protein that meets the structural limitations of claims 26 and 35 as well as a nucleic acid molecule which meets the limitations of claims 32 and 36 (sequence similarity to SEQ ID NO:3). Figure 7 of Tischer et al. teaches a nucleic acid molecule which has 68% similarity to SEQ ID NO:3 of the instant application over a span of 174 nucleotides (see attached sequence alignment). The overall alignment of the sequences only results in a match of 4.4%, but the claims do not state how the alignment or sequence comparison is to be calculated, therefore, the nucleic acid molecule of Tischer et al. anticipates the instant claims. As stated above, Tischer et al. further teach a method of making a protein using the nucleic acid molecule, thereby meeting the limitations of claims 35-36.

19. Claims 26-33 and 35-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Eriksson et al. (U.S. Pat. No. 5,607,918).

Claim 29 requires that the nucleic acid molecule encode an amino acid sequence "as substantially as set forth in SEQ ID NO:6". Eriksson et al. teach a nucleic acid molecule (see Figure 10, SEQ ID NO:10) which encodes a protein having the amino acid sequence of SEQ ID NO:6 (see Figure 11 of Eriksson et al. and attached sequence comparison to the reference - SEQ ID NO:11 of Eriksson et al. is the same as that of SEQ ID NO:6 of the instant application). Eriksson et al. claims priority to U.S.S.N. 08/397,651, which has a filing date of 01 March 1995, and therefore, constitutes prior art against the instant application.

Claims 26 and 31 require that the percentage similarity at the protein level be at least 30%. The protein of Eriksson et al. of SEQ ID NO:11 is approximately 34% similar, and therefore, meets this limitation of the claims. The sequence similarity of the nucleic acid molecule must be at least 15% with at least about 30% dissimilarity (see claims 32 and 36). The nucleic acid molecule of Eriksson et al. which encodes the protein of SEQ ID NO:11 is SEQ ID NO:10 and has about 38% similarity over the entire nucleic acid molecule sequence (see sequence comparison attached to the reference). Eriksson et al. further teach methods of expressing a protein using the nucleic acid molecules (see column 10, lines 14-28). Therefore, the claims are anticipated by the prior art.

Claim 33 of the instant application requires the nucleic acid molecule to encode a "murine homologue of human VEGF" and comprise a nucleotide sequence "substantially as set forth in Figure 9". The nucleotide sequence of Figure 9 is SEQ ID NO:16 and encodes a protein having a sequence of SEQ ID NO:17. The protein of SEQ ID NO:17 is the same protein as taught by Eriksson et al. in Figure 12 of SEQ ID NO:5. Therefore, Eriksson et al. teach a nucleotide sequence substantially as set forth in Figure 9 in that it encodes the same protein as Figure 9 and therefore, is substantially as set forth.

Conclusion

20. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 3PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

January 3, 1999

Christine Saoud, Ph.D.
Christine Saoud
Patent Examiner
Art Unit 1646